Advanced Pharmaceutical Technology

Liquid Crystals in Drug Delivery

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Introduction

- Approximately 40% of currently marketed compounds and most current drug development candidates remain poorly water soluble
- This is likely to result in poor absorption and bioavailability, insufficient solubility for IV dosing, developmental challenges, and harm to the patient (frequent high dose administration)

Introduction

- Liquid crystalline (LC) drug delivery systems have gained considerable attention in the last few decades as a multifunctional technique that may have the capability to both enhance the solubility and control the drug release rate
- These systems started out predominantly for topical administration in the early 1980s, but have now been expanded to oral and parenteral administration

What are liquid crystals (LC)?

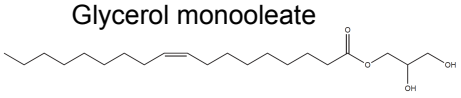
- A liquid crystal is a state of matter that exhibits properties between **a conventional liquid** and **a solid crystal**
- LC state can be subdivided into two types: lyotropic and thermotropic
- **Thermotropic** liquid crystals exhibit properties dependent on the applied temperature of the system
- **Lyotropic** liquid crystalline systems are based upon the self-assembly of amphiphilic molecules induced by a solvent (typically aqueous)

What are liquid crystals (LC)?

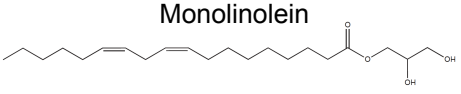
- The architecture of the system depends on:
  - The amphiphile's structure
  - Additives used
  - Temperature
  - pH
  - Water content
  - Salt concentration
- Due to the amphiphilic nature of LC systems, hydrophilic, lipophilic, or amphiphilic molecules can be encapsulated
- Lyotropic LC are the type mostly used for drug delivery

Commonly used LC forming materials

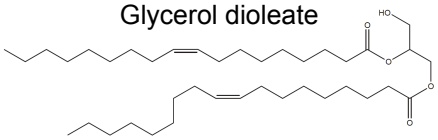
Glycerol monooleate



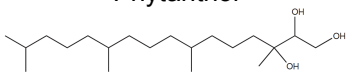
Monolinolein



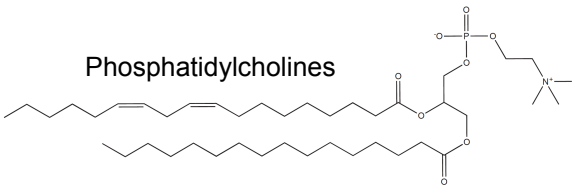
Glycerol dioleate



Phytantriol

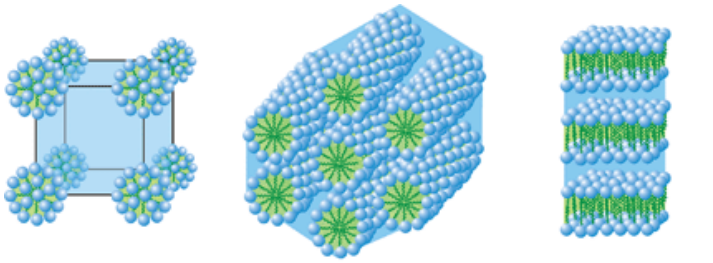


Phosphatidylcholines



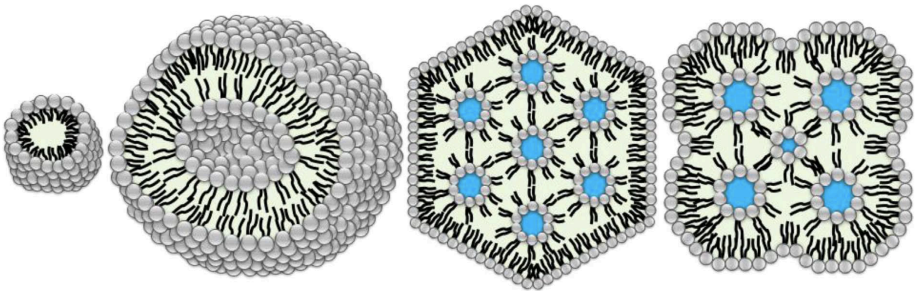
Lyotropic liquid crystals (LLC)

- LLC take many shapes, most commonly lamellar, cubic, and hexagonal mesophases
- Those can be normal or reversed
- Reversed phases are useful for controlled drug release
- The amphiphilicity of the drug molecule will determine the location in the liquid crystalline matrix



cubic phase I_1 hexagonal phase H_1 lamellar phase L_α

Lyotropic liquid crystals (LLC)



Left to right: micelle, liposome, reversed hexagonal LLC, and reversed cubic LLC

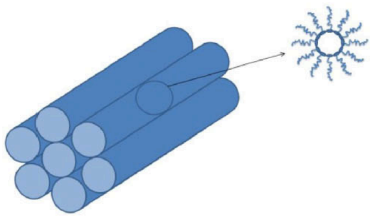
Phase behaviors of LLC

- Molecular geometry of the amhiphile has an important role in determining mesophase behavior
- This can be described by the critical packing parameter (CPP)
- CPP = V/A.L
  - V = volume of the hydrophobic chain
  - A: cross-sectional area of the head group
  - L: length of the hydrophobic chain
- Depending on CPP, different self-assembled structures can be formed

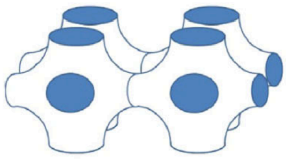
Phase behaviors of LLC

CPP > 1

H_2



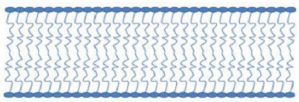
Q_2



Phase behaviors of LLC

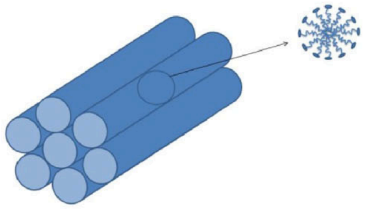
CPP = 1

L_α



CPP < 1/3

H_1



Reversed cubic and hexagonal mesophases

- Reversed cubic and hexagonal mesophases are often formed by polar lipids in an aqueous environment
- The structure-forming lipids can absorb a certain amount of water and then spontaneously form gel-like phases with unique internal structures, into which drugs can be incorporated
- Reversed cubic and hexagonal mesophases can also form colloidal dispersions (nanoparticles) with superior thermodynamic stability – cubosomes and hexosomes

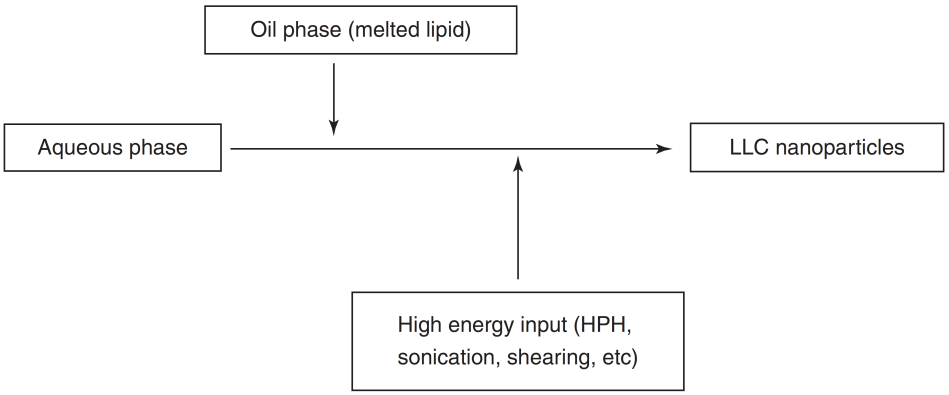
Reversed cubic and hexagonal mesophases

- Cubic and hexagonal LLC gels can be prepared by simply blending aqueous phase with lipid phase using vortex or ultrasonication
- The manufacture of cubosomes or hexosomes is more complicated
- Top-down vs. bottom-up approach

Top-down approach

- The LC bulk phase (viscous gel) is prepared by mixing structure-forming lipids with stabilizers
- The resultant mass is dispersed into aqueous solution by high-pressure homogenization, sonication, or shearing to form LLC nanoparticles
- This approach requires several cycles to achieve the desired nanoparticles with appropriate characteristics
- High-energy input is incompatible with temperature sensitive ingredients
- The cubosomes prepared through top-down approach are always observed to coexist with vesicle-like structures (unilamellar liposomes)

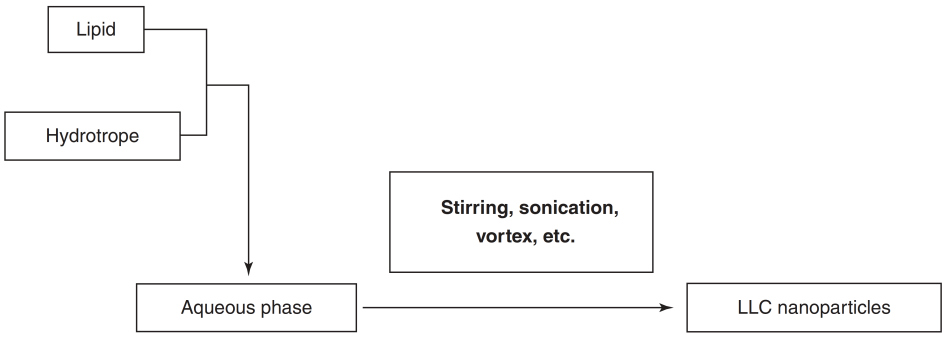
Top-down approach



Bottom-up approach

- Depends on using a "hydrotrope"
- Hydrotrope: an agent which can dissolve the lipid phase to create highly concentrated liquid precursors
- This mixture is added to the aqueous phase → stirring, vortex, or sonication (but milder conditions than the top down approach) → LLC nanoparticles
- This method requires less energy input and it is far more efficient at generating small particles than the top-down approach
- The particles formed are also more stable, but may coexist with vesicles

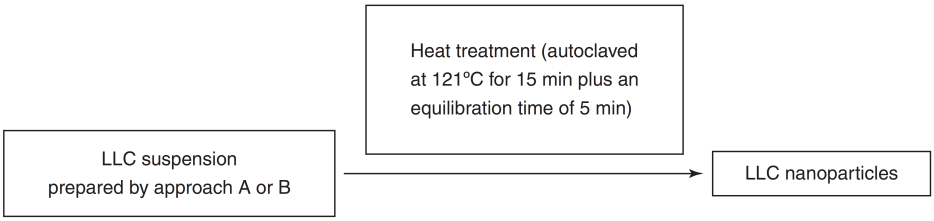
Bottom-up approach



Heat treatment

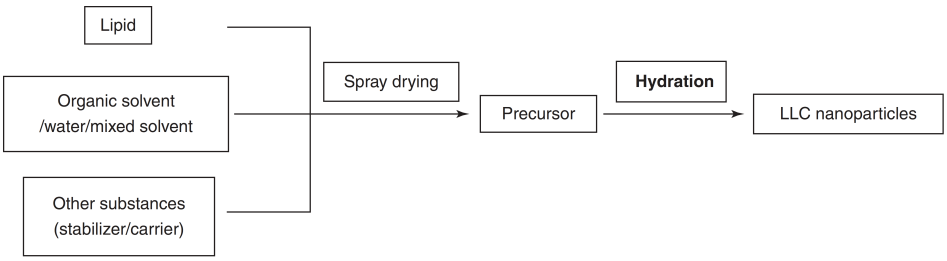
- Used after top-down or bottom-up methods to get rid of vesicles
- Heat treatment promotes the transformation from non-cubic vesicles to well-ordered cubic particles
- One explanation is the decrease in stabilizer (i.e. surfactant) solubility at higher temperature, forcing the vesicles to fuse together and join the cubic nanoparticles
- But this method is not suited for heat-labile drugs

Heat treatment


Heat treatment (autoclaved at 121°C for 15 min plus an equilibration time of 5 min)
LLC suspension prepared by approach A or B
LLC nanoparticles

Spray drying

- Used to prepare dry powder LLC nanoparticles
- The lipid ± organic solvent and excipients are are mixed with water to form a solution/dispersion → spray drying → powder can be rehydrated to form LLC
- Better long term stability but with residual solvent concerns



Drug release from LLC

- Bulk cubic and hexagonal mesophases have been investigated as sustained drug delivery systems for almost 30 years
- In most cases release has been shown to follow Higuchi diffusion-controlled kinetics
- The release behavior is related to many aspects, such as the properties of drugs, initial water content, type of LLC phases, drug loading, interactions between the drug and lipid bilayers, among others
- In case of dispersed phases (cubosomes and hexosomes), they tend to show a burst initial release due to the increase in surface area

Parenteral administration of LLC

- Reversed cubic and hexagonal phases are highly viscous, which makes them difficult to inject
- Approaches to overcome this problem include using flowable precursors and LLC nanoparticles
- For some structure-forming lipids, the transition from lamellar phases (more fluid) to cubic phases can be completed upon heating from room temperature to body temperature or by absorbing water

Parenteral administration of LLC

- Upon SC or IM injection, lamellar phases will gradually absorb water from body fluids or surrounding tissues and, subsequently, convert to cubic phases → sustained release depot
- Cubosomes and hexosomes are particularly suitable for IV injection due to their small size, low viscosity, and thermodynamic stability

Oral administration of LLC

- The main challenge for the use of LC as oral sustained release formulations in vivo is GIT stability and resistance to digestive processes
- Ex. Glyceryl monooleate (GMO) is sensitive to digestive enzymes
- More novel materials such as phytantriol (PT) and oleyl glycerate (OG) are resistant to enzymatic degradation → sustained drug release and enhancement in bioavailability

Topical application of LLC

- Many studies have shown that cubic and hexagonal mesophase formulations are capable of penetrating through the stratum corneum (rate-limiting step in skin permeation)
- At present, GMO-based and PT-based mesophases are the most widely investigated LLC systems for topical drug delivery
- Advantages of LLC for topical drug delivery:
  1. Sustained drug release
  2. Bioadhesive properties
  3. Solubilization of hydrophilic and lipophilic drugs and protecting them from physical and enzymatic degradation
  4. Structure-forming lipids can act as nontoxic permeation enhancers

Mucosal drug delivery using LLC

- The structure-forming materials of LLC possess at least two hydroxyl groups, which make them available for hydrogen bonding to mucus membranes
- Therefore, cubic and hexagonal mesophases are good candidates for mucosal drug delivery
- To facilitate application, flowable precursors are employed, which can form the viscous cubic or hexagonal gels by absorption of body fluids or temperature change in vivo
- LLC dispersions (cubosomes and hexosomes) can also be used and will likely exhibit enhanced performance compared to the bulk mesophases

Case studies

- Bisset, N.B., et al. *Tailoring liquid crystalline lipid nanomaterials for controlled release of macromolecules*. Int. J. Pharm 2015, 495(1), 241-248
- Zhang, Y., et al. *Transdermal baicalin delivery using diethylene glycol monoethyl ether-mediated cubic phase gel*. Int. J. Pharm 2015, 479(1), 219-226
- von Halling Laier, C., et al. *Spray dried cubosomes with ovalbumin and Quil-A as a nanoparticulate dry powder vaccine formulation*. Int. J. Pharm 2018, 550(1-2): 35-44